

To:
 PETER P. CORLESS
 EDWARDS & ANGEL, LLP
 P.O. BOX 55874
 BOSTON, MA 02205

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 62799-PCT (71699)	Date of mailing (day/month/year) 27 MAY 2005
International application No. PCT/US05/03368	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant JOHN HOPKINS UNIVERSITY	International filing date (day/month/year) 04 February 2005 (04.02.2005)

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.
- Filing of amendments and statement under Article 19:**
 The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):
- When?** The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.
- Where?** Directly to the International Bureau of WIPO, 34 chemin des Colombettes
 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 740 14 35
- For more detailed instructions, see the notes on the accompanying sheet.
2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.
4. **Reminders**
- Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.
- The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.
- Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.
- In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.
- See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Jeffrey T. Barton Jean-Pierre Paralega Telephone No. (571)272-1307
--	--

Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)

BEST AVAILABLE COPY

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 62799-PCT (71699)	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US05/03368	International filing date (<i>day/month/year</i>) 04 February 2005 (04.02.2005)	(Earliest) Priority Date (<i>day/month/year</i>) 04 February 2004 (04.02.2004)
Applicant JOHN HOPKINS UNIVERSITY		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐

With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box No. II)

3. ☐ Unity of invention is lacking (See Box No. III)

4. With regard to the title,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____



as suggested by the applicant.



as selected by this Authority, because the applicant failed to suggest a figure.



as selected by this Authority, because this figure better characterizes the invention.

- b. ☒

none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/03368

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : G01N 27/26, 27, 447

US CL : 204/547, 643

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 204/547, 643

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/0098248 A1 (VOGEL et al) 29 May 2003 (29.05.2003), Entire document.	1-14
X	US 2002/0088712 A1 (MILES) 11 July 2002 (11.07.2002), Entire document.	1-4 and 6-13
—		5 and 14
Y		5 and 14
Y	WO 03/093791 A2 (ALBRITTON et al) 13 November 2003 (13.11.2003), Especially paragraphs 053 and 060.	1-3 and 6-12
X	US 6,440,285 B1 (FUHR) 27 August 2002 (27.08.2002), Entire document.	1, 2, and 6-12
X	US 2002/0125138 A1 (MEDORO) 12 September 2002 (12.09.2002), Entire document.	3
—		
Y		

Further documents are listed in the continuation of Box C.

☐

See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

04 May 2005 (04.05.2005)

Date of mailing of the international search report

27 MAY 2005

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Authorized officer

Jeffrey T. Barton

Telephone No. (571)272-1307

Jean Proctor
Paralegal Spec.

To:
PETER P. CORLESS
EDWARDS & ANGEL, LLP
P.O. BOX 55874
BOSTON, MA 02205

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year) **27 MAY 2005**

Applicant's or agent's file reference

62799-PCT (71699)

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US05/03368

International filing date (day/month/year)

04 February 2005 (04.02.2005)

Priority date (day/month/year)

04 February 2004 (04.02.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): G01N 27/26, 27, 447 and US Cl.: 204/547, 643

Applicant

JOHN HOPKINS UNIVERSITY

1. This opinion contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|--|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the opinion |
| <input type="checkbox"/> | Box No. II | Priority |
| <input type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input checked="" type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input type="checkbox"/> | Box No. VIII | Certain observations on the international application |

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703) 305-3230

Authorized officer

Jeffrey T. Barton

Telephone No. (571)272-1307

Jean Proctor
Paralegal Specialist

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application no.
PCT/US05/03368

Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>NONE</u>	YES
	Claims <u>1-14</u>	NO
Inventive step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-14</u>	NO
Industrial applicability (IA)	Claims <u>1-14</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Please See Continuation Sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

international application no.

PCT/US05/03368

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claim 5 is objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: there is no antecedent basis in claim 1 for "the cell-adhesive region". The claim is treated as dependent on claim 4, which would remedy this defect.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

Claims 1-8, and 10-14 lack novelty under PCT Article 33(2) as being anticipated by Vogel et al.

Regarding claim 1, Vogel et al disclose an apparatus for arraying particles (e.g. Example 5; Multiaperture system shown in Figures 6 and 7), comprising: a substrate comprising an array of electrodes (Figures 6 and 7; substrate 192, electrodes 196a; alternatively positioned above the substrate body on a spacer as in electrode 76a of Figure 3; See Examples 2 and 5 and Paragraph [0078]); a counter-electrode plate substantially parallel to the array of electrodes (196b on plate 206; single planar plate electrode disclosed in Figure 3, electrode 76b); and a fluid inlet for permitting a particle-containing fluid to flow between the array of electrodes and the counter electrode. (Paragraph [0109] describes positioning, [0098] describes sample handling system; flow of a sample to the aperture is necessary and inherent in the functioning of the device, and such flow takes place between the electrode array and the electrode plate)

Regarding claim 11, Vogel et al disclose using the apparatus described above in addressing claim 1 in a method comprising the steps: flowing a particle containing fluid between the array of electrodes and the counter-electrode plate (Paragraphs [0109] and [0132]); and subjecting the fluid to an electric field by applying an electric potential to the array of electrodes under conditions such that particles in the fluid are arrayed. (Paragraph [0109])

Regarding claims 2 and 3, Vogel et al disclose a voltage source for applying a field between the electrodes 76a-76b or 196a-196b, the disclosed field being less than 100 volts/mm. (Paragraphs [0075]-[0080]; Field of 0.1 V/mm or greater disclosed in [0079])

Regarding claims 4, 5, and 12-14, Vogel et al disclose the particles being cells (e.g. paragraph [0103]), and the apparatus comprising cell adhesive regions comprising collagen and fibronectin (Paragraphs [0059]-[0068], particularly [0063]), and non-adhesive regions. (Figure 7, regions with hydrophobic coat 204 described in Paragraph [0144])

Regarding claim 6, Vogel et al disclose a fluid outlet. (Paragraph [0098] - describes a sample handling system for adding and removing samples from the device)

Regarding claims 7 and 8, Vogel et al disclose an array of over 1000 electrodes. (Table within Paragraph [0085]; each site requires one electrode in the array)

Regarding claim 10, Vogel et al disclose independently addressing each electrode of the array. (Paragraph [0145])

Claim 9 lacks an inventive step under PCT Article 33(3) as being obvious over Vogel et al.

Vogel et al disclose an apparatus as described above in addressing claim 1. They also disclose electrodes with diameters as low as 100 microns. (Paragraph [0135])

Vogel et al do not explicitly disclose electrodes with diameters less than 100 microns.

It would have been obvious to one having ordinary skill in the art to modify the apparatus of Vogel et al by using electrodes with diameters below 100 microns, because Vogel et al disclose and suggest the miniaturization of components of their system, in order to accommodate more measurement sites within a given area (e.g. Paragraphs [0085], [0256], and [0304]), and scaling of the system to 9600 measurement sites or more as suggested in Paragraph [0085] would require appropriate scaling of features such as electrodes and the lead wires connecting them. A skilled artisan would be motivated and able to make the smaller electrodes required

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

by such scaling.

Claims 1, 2, 4, 6, and 10-13 lack novelty under PCT Article 33(2) as being anticipated by Miles.

Regarding claim 1, Miles discloses an apparatus for arraying particles (e.g. Figure 4; Abstract; Paragraph [0004]; the term "arraying" is read broadly to mean the disposition of a plurality of particles on the substrate in any fashion, as would be the case in the concentration of particles disclosed by Miles), comprising: a substrate comprising an array of electrodes (Figure 4; electrodes 12-20; Paragraph [0020]), electrodes are disposed on a substrate that defines a channel wall); a counter-electrode plate substantially parallel to the array of electrodes (23); and a fluid inlet for permitting a particle-containing fluid to flow between the array of electrodes and the counter electrode. (e.g. Figure 6, sample inlet 56; Paragraph [0020] describes the electrodes being disposed in a flow channel, and any such channel must have an inlet for the sample)

Regarding claim 11, Miles discloses using the apparatus described above in addressing claim 1 in a method comprising the steps: flowing a particle containing fluid between the array of electrodes and the counter-electrode plate (Paragraph [0020]; flow of a fluid comprising the particles into the channel is inherent in the method); and subjecting the fluid to an electric field by applying an electric potential to the array of electrodes under conditions such that particles in the fluid are arrayed on the surface of the substrate. (Paragraph [0019]; the term "arrayed" is read broadly to mean the disposition of a plurality of particles on the substrate in any fashion, as would be the case in the concentration of particles disclosed by Miles)

Regarding claim 2, Miles discloses a voltage source for applying a field between the electrodes. (Paragraph [0023])

Regarding claims 4, 12, and 13, Miles discloses the particles being cells (e.g. paragraph [0019]), and the apparatus comprising cell adhesive regions and non-adhesive regions. (e.g. Figures 3 and 4; Paragraph [0023] disclose cells adhering to electrodes 12-20, not adhering to other surfaces, such as electrode 23. This reads on the claim limitations.)

Regarding claim 6, Miles discloses a fluid outlet. (e.g. Figure 6, exit 61'; Paragraph [0020] describes the electrodes being disposed in a fluid flow channel, and any such channel must have an outlet)

Regarding claim 10, Miles discloses independently addressing each electrode of the array. (Paragraph [0023])

Claims 3 and 7-9 lack an inventive step under PCT Article 33(3) as being obvious over Miles.

Miles discloses an apparatus as described above in addressing claims 1 and 2.

Miles does not explicitly disclose any particular voltage to be applied between the electrodes, any desired number of electrodes, or desired electrode dimensions.

Regarding claim 3, it would have been well within the skill of one having ordinary skill in the art at the time the invention was made to select an appropriate voltage for use in manipulating the particles. Additionally, a skilled artisan would have recognized that the range of useful field strengths would include those below 100 V/mm.

Regarding claims 7 and 8, it would have been obvious to one having ordinary skill in the art at the time the invention was made to choose any number of electrodes to be disposed opposite electrode 23, depending on the size and complexity of the device and sample mixture to be manipulated. Miles only disclosed a general "set" of electrodes (Paragraph [0022]), without specifying how many were desired, and a skilled artisan would recognize that the device and method of Miles could be used with fifty, one hundred, or even more electrodes.

Regarding claim 9, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use any desired electrode size within the device. Since the size of cells is on the order of tens to hundreds of microns, a skilled artisan would have recognized that electrodes of this size would allow very precise manipulations. Furthermore, Miles discloses that the electrodes are deposited photolithographically (Paragraph [0022]), and one skilled in the photolithographic art at the time of the invention would have known that deposition of metal electrodes with cross-sectional dimensions of tens of microns was within the level of ordinary skill in this art.

Claims 5 and 14 lack an inventive step under PCT Article 33(3) as being obvious over Miles in view of Albritton et al.

Miles discloses an apparatus as described above in addressing claims 1, 4, and 13.

Miles does not explicitly disclose a cell adhesion region comprising a layer of fibronectin or collagen.

Albritton et al disclose a cell arraying device wherein adhesion of the cells to a desired region is aided by the provision of a cell adhesion layer, which can comprise collagen or fibronectin. (e.g. Paragraphs [053] and [060])

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the apparatus of Miles by providing a cell adhesion layer comprising collagen or fibronectin at a selected area within the apparatus, as taught by Albritton et al, because it would aid in the secure collection of cells in that selected area. Miles discloses such collection of a plurality of cells as one of the objects of the invention. (Paragraph [0011])

Claims 1-3, 6, and 9-12 lack novelty under PCT Article 33(2) as being anticipated by Fuhr.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US05/03368

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Regarding claim 1, Fuhr discloses an apparatus for arraying particles (Abstract; "arranging objects at predetermined positions" reads on "arraying"), comprising: a substrate comprising an array of electrodes (Column 3, line 66 - Column 4, line 3); a counter-electrode plate substantially parallel to the array of electrodes (Column 3, line 66 - Column 4, line 3; the second plate reads on this limitation); and a fluid inlet for permitting a particle-containing fluid to flow between the array of electrodes and the counter electrode. (Column 3, line 66 - Column 4, line 3; Column 4, lines 8-10 - a fluid inlet is necessary and inherently present)

Regarding claim 11, Fuhr discloses using the apparatus described above in addressing claim 1 in a method comprising the steps: flowing a particle containing fluid between the array of electrodes and the counter-electrode plate (Column 4, lines 8-19); and subjecting the fluid to an electric field by applying an electric potential to the array of electrodes under conditions such that particles in the fluid are arrayed on the surface of the substrate. (Abstract; Column 2, lines 28-44 - such collection of particles in the device reads on the particles being arrayed on the substrate surface)

Regarding claims 2 and 3, Fuhr discloses a voltage source for applying a field between the electrodes, the disclosed field being less than 100 volts/mm. (Column 5, lines 11-37; in order for the device to function, the distance between electrodes could not be greater than mm scale)

Regarding claim 6, Fuhr discloses a fluid outlet. (Column 3, line 66 - Column 4, line 3; Column 6, lines 56-63; an outlet is inherent in such a flow-through device)

Regarding claim 9, Fuhr discloses electrodes formed with nanometer to micrometer cross-sectional dimensions. (Column 4, lines 4-7)

Regarding claim 10, Fuhr discloses independently addressing each electrode of the array. (Column 5, lines 11-29; Table 1)

Regarding claim 12, Fuhr discloses manipulating cells. (e.g. Column 2, lines 63-66)

Claims 7 and 8 lack an inventive step under PCT Article 33(3) as being obvious over Fuhr.

Fuhr discloses an apparatus as described above in addressing claim 1.

Fuhr does not explicitly disclose any desired number of electrodes.

Regarding claims 7 and 8, it would have been obvious to one having ordinary skill in the art at the time the invention was made to choose any number of electrodes to be used in the device of Fuhr, depending on the size and complexity of the device and sample mixture to be manipulated. Fuhr discloses variability in number and positioning of the electrodes (e.g. Column 4, lines 40-42) without specifying how many were desired, and a skilled artisan would recognize that the device and method of Miles could be used with fifty, one hundred, or even more electrodes. For example, if arrangements such as that shown in Figure 3 were used for parallel sorting procedures in order to improve throughput, the limitations of these claims would be met.

Claims 1, 2, and 6-12 lack novelty under PCT Article 33(2) as being anticipated by Medoro.

Regarding claim 1, Medoro discloses an apparatus suitable for arraying particles comprising: a substrate comprising an array of electrodes (Figure 1, substrate O1, electrodes LIJ); a counter-electrode plate substantially parallel to the array of electrodes (M2); and a fluid inlet for permitting a particle-containing fluid to flow between the array of electrodes and the counter electrode. (Paragraph [0098])

Regarding claim 11, Medoro discloses using the apparatus described above in addressing claim 1 in a method comprising the steps: flowing a particle containing fluid between the array of electrodes and the counter-electrode plate (Paragraph [0098]); and subjecting the fluid to an electric field by applying an electric potential to the array of electrodes under conditions such that particles in the fluid are arrayed on the surface of the substrate. (Abstract; Paragraphs [0106]-[0107] - such collection of particles in the cages above the substrate reads on the particles being arrayed on the substrate surface)

Regarding claim 2, Medoro discloses a voltage source for applying a field between the electrodes. (Paragraph [0067])

Regarding claim 6, Medoro discloses a fluid outlet. (Paragraph [0098] - means for introducing fluid can also be used for removing it)

Regarding claims 7 and 8, Medoro discloses over 100 electrodes. (Paragraph [0061])

Regarding claim 9, Medoro discloses electrodes with cross-sectional dimensions less than 100 microns. (Paragraph [0061])

Regarding claim 10, Medoro discloses independently addressing each electrode of the array. (Paragraph [0061] describes "selectively addressable electrodes"; Paragraphs [0069] - [0085] describe formation of cages)

Regarding claim 12, Medoro discloses manipulating cells. (Paragraph [0010])

Claim 3 lacks an inventive step under PCT Article 33(3) as being obvious over Medoro in view of Fuhr.

Medoro discloses an apparatus as described above in addressing claim 2.

Medoro does not explicitly disclose using an electric field strength below 100 V/mm.

Fuhr discloses a similar device using potential cages to trap and manipulate particles, in which he uses electric field strengths below 100 V/mm. (Column 5, lines 11-37; in order for the device to function, the distance between electrodes could not be greater

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US05/03368

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

than mm scale, which would lead to a field strength below 100 V/mm)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to select an appropriate voltage for use in manipulating and trapping the particles. Additionally, a skilled artisan would have recognized that the range of useful field strengths would include those below 100 V/mm, given the disclosure of Fuhr.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☒ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☒ **FADED TEXT OR DRAWING**
- ☒ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER: _____**

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.